What Lies Ahead? Exploring Future ADC Targets of Interest

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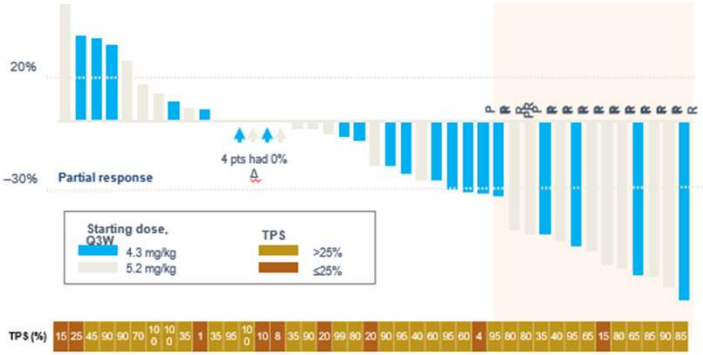
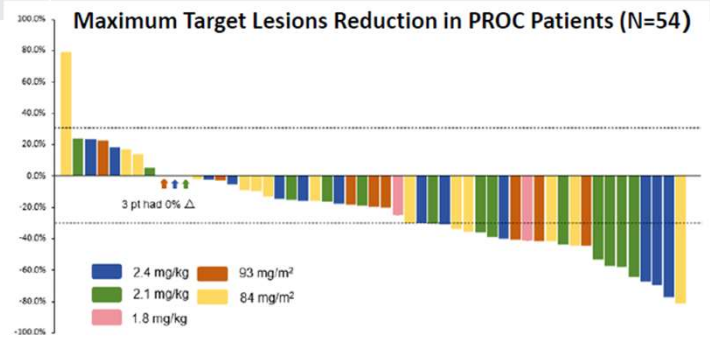
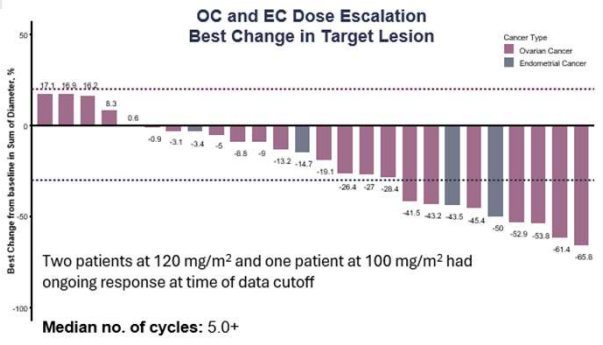
Targeting FRα in Ovarian Cancer: What is next?

	Luveltamab Tazevibulin NCT03748186	BAT-8006 NCT05378737	Rinatabart sesutecan NCT05579366
Payload	SC-209 – Hemiasterelin derivative cytotoxic	Exatecan	Exatecan
ORR	43.8% FRα >25% by TPS (5.2mg/kg) 31.2% (4.3mg/kg)	37% All FRα 39%> 50% FRα 46.7% > 75% FRα	50% (n=18 at 120mg/m2)
mPFS	FRα > 25% 6.1 (95% CI 4.1- 7.2)	7.47 (4.27- NR)	NR
mOS	NR	NR	NR







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Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May-4 June 2024; Chicago, IL USA.; Jia F, et al. Presented at: ASCO 2024.; Lee E, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.; Shapira-Frommer R, et al. Presented at: ESMO 2024. [Abstract 754P].

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Luveltamab tazevibulin (STRO-002)
REFRaME-01: Phase 2/3 Pivotal Trial in PROC
ongoing[1,2]

Eligibility

- **Platinum Resistant Ovarian Cancer** to first platinum or progression ≤ 6m to last platinum
- 1–3 prior lines
- ECOG PS 0–1
- Exclude primary platinum refractory
- FolR1 expression ≥ 25%

Phase 2: Dose Finding

R 1:1

- N = 25 → Dose A: 5.2 mg/kg IV q3W + prophylactic G-CSF 4.3 mg/kg after 2 cycles
- N = 25 → Dose B: 4.3 mg/kg IV q3W

Phase 3: Randomized Trial

R 1:1

- N = ~258 → Optimized Dose Regimen
- N = ~258 → Investigator's Choice Chemotherapy

Key Endpoints

- Final analysis for full approval: PFS, OS
- Interim analysis planned to support accelerated approval: ORR, DOR
- Safety, QoL, PK

NCT05870748

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Figure adapted from Oaknin A, et al.[2]

1. NCT05870748. Accessed 15.06.2024 from: https://clinicaltrials.gov/study/NCT05870748.; 2. Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May-4 June 2024; Chicago, IL USA [Abstract TPS5637].

Luveltamab tazevibulin (STRO-002)
REFRaME-01: Phase 2/3 Pivotal Trial in PROC, *ongoing*[1,2]

Sutro Biopharma Announces Selected Dose for Luvelta and Topline Results from Dose-Optimization Portion of REFRαME-O1 Trial in Platinum Resistant Ovarian Cancer[3]

Dec 10, 2024

– 32% objective response rate (ORR) in evaluable patients at the 5.2 mg/kg starting dose – the selected dose for randomized portion (Part 2) of ongoing registrational REFRαME-O1 trial –

NCT05870748

Figure adapted from Oaknin A, et al.[2]

1. NCT05870748. Accessed from: https://clinicaltrials.gov/study/NCT05870748.; 2. Oaknin A, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 31 May-4 June 2024; Chicago, IL USA [Abstract TPS5637].; 3. https://www.sutrobio.com/sutro-biopharma-announces-selected-dose-for-luvelta-and-topline-results-from-dose-optimization-portion-of-refr%ce%b1me-o1-trial-in-platinum-resistant-ovarian-cancer/.

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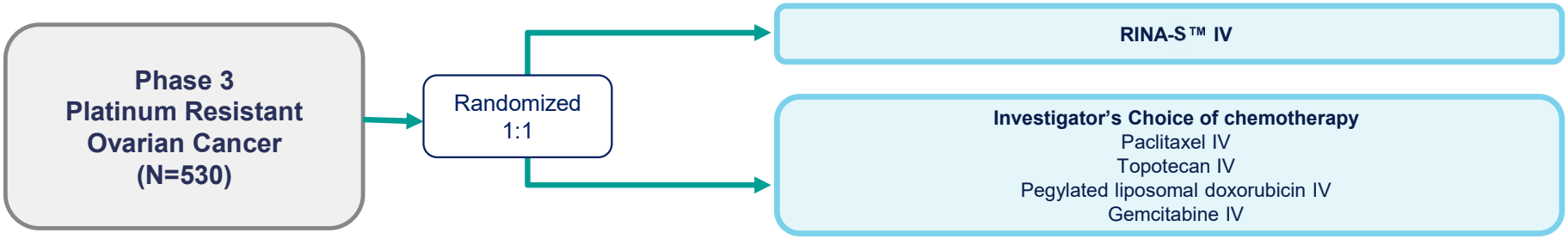
Efficacy of Rina-S Compared to Treatment of Investigator's Choice in Participants with PROC: ENGOT-OV86/GOG 3107/ RAINFOL-OV2



Evaluation of Study Objectives*

Primary Outcome Measure

- Progression-Free Survival

Secondary Outcome Measures

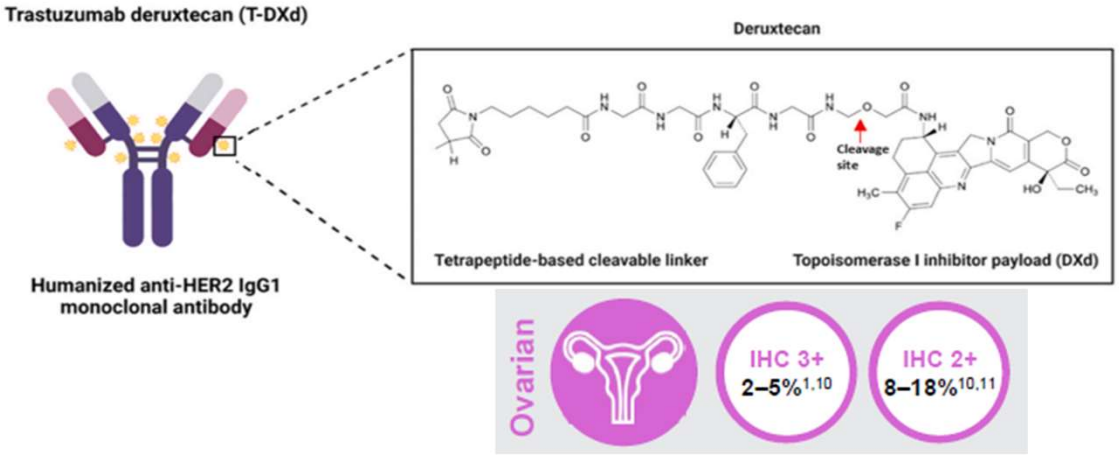
- Overall Survival
- Objective Response Rate
- Duration of Response
- CA-125 response by GCIG criteria
- Adverse Events
- GHS/QoI (EORTC-QLQ-C30)

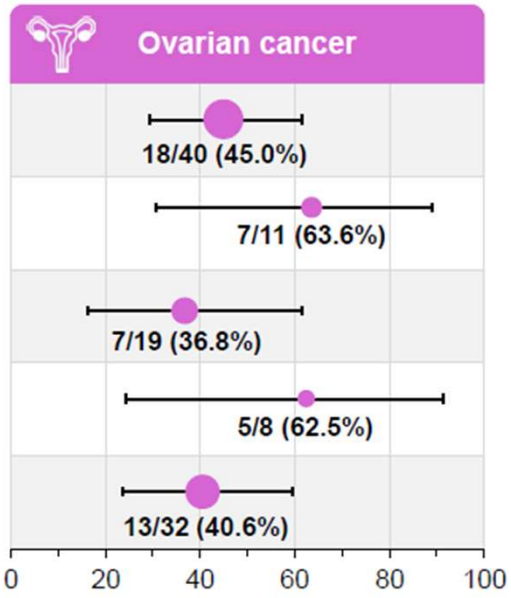
Key Inclusion Criteria*

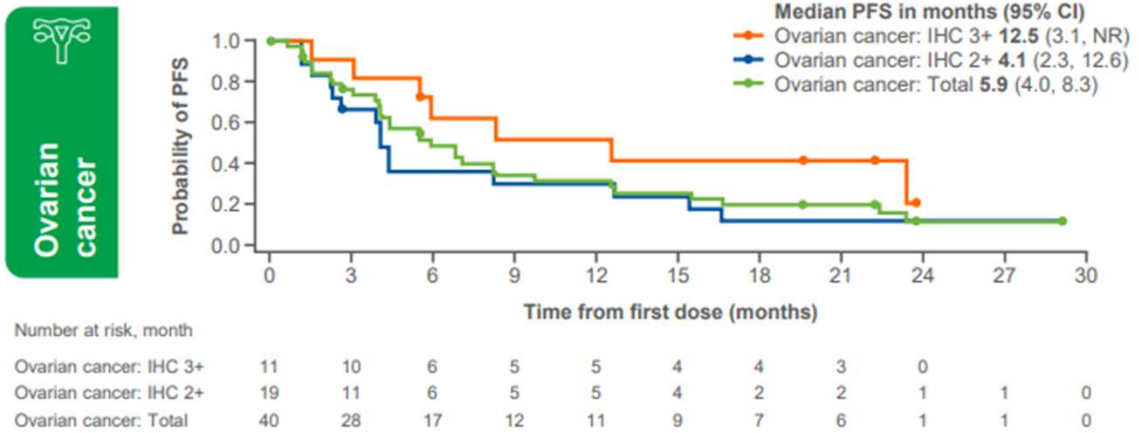
- Histologically or cytologically confirmed high grade serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- Prior treatment with the following:
  - Platinum-based therapy
  - Bevacizumab (unless contraindicated)
  - PARP inhibitor (if known BRCA mutation)
  - Mirvetuximab (if positive FRα expression and available in the region)
- Platinum-resistant disease
- No prior ADC therapy containing a topoisomerase 1 inhibitor
- No known active central nervous system metastases or carcinomatous meningitis

Targeting HER2 in Ovarian Cancer: What do we know so far?

	Trastuzumab deruxtecan (DS-8201)[1-4]
Payload	Topoisomerase 1 inhibitor (DXd)
DAR	8
Linker	Cleavable tetrapeptide based linker
Trial	NCT04707248







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Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. doi: 10.1200/JCO.23.02005.

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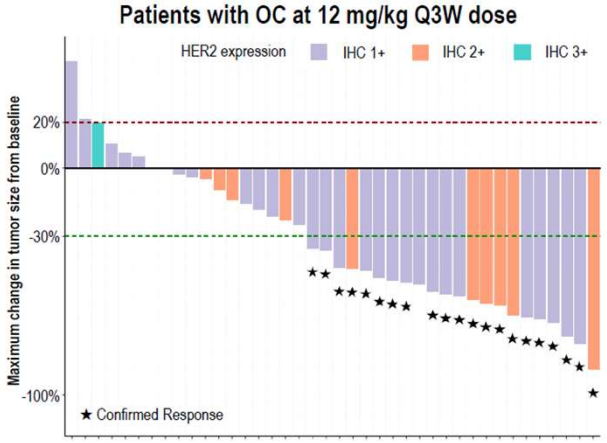
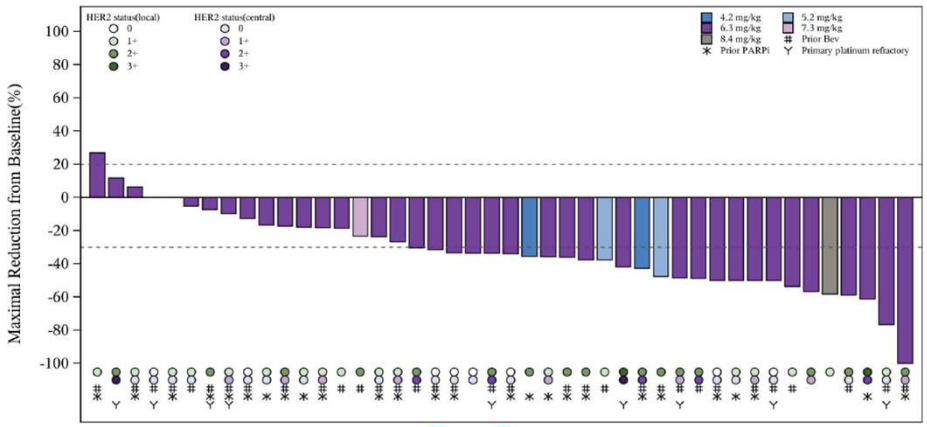
Targeting HER2 in Ovarian Cancer: What is Next?

	IBI354 (n=40 at 12mg/kg q 3 w)	JSKN003 N=27
Payload	NT3 (a topoisomerase I inhibitor)	Topoisomerase I inhibitor
Trial	NCT05636215	NCT05494918/NCT05744427
ORR	52.5% (95% CI 36.1-68.5) 3+ (only 1 pt) 2+ 50% (95% CI 21.1 – 78.9) 1+ 55.5% (95% CI 35.3-74.5)	59% (95%CI 36.4-79.3)
mDOR	Not reached	6.03 months *(immature)*
mPFS	6.8 months (95% CI 5.2 – NR)	9.43 months *(immature)*





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1. Shu J, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain [Abstract 720M0].; 2. Rao Q, et al. Presented at: ESMO 2024. [Abstract 759P].

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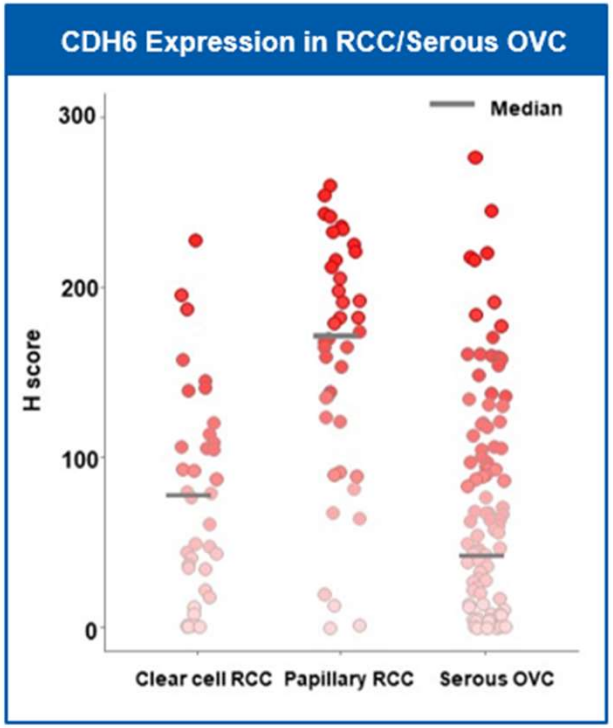
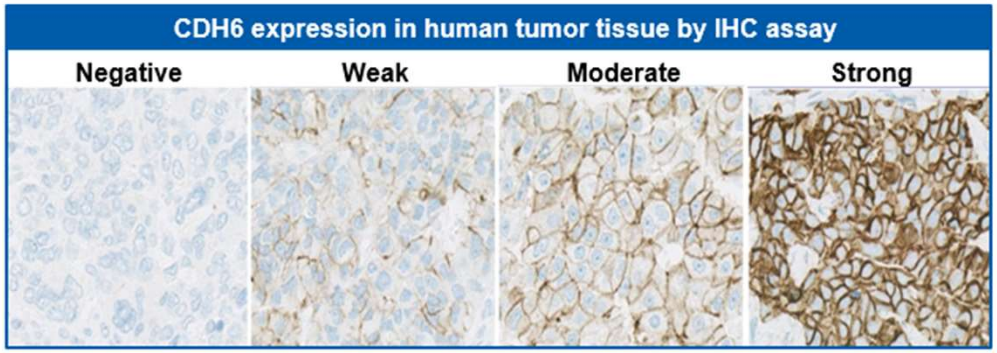
Targeting Cadherin 6 (CDH6) in Ovarian Cancer: Why?





Tumor type	n	CDH6 H-score (n ,%)							
		0		1-100		101-200		201-300	
Clear cell RCC	39	0	0%	25	64%	13	33%	1	3%
Papillary RCC	41	1	2%	9	22%	18	44%	13	32%
Serous OVC	118	18	15%	71	60%	24	20%	5	4%

- CDH6 is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- Function of CDH6 has yet to be fully elucidated
- CDH6 is overexpressed in various cancers, particularly EOC

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Hirokazu S, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 16-21 September 2021; Paris, France. [Abstract 10P].

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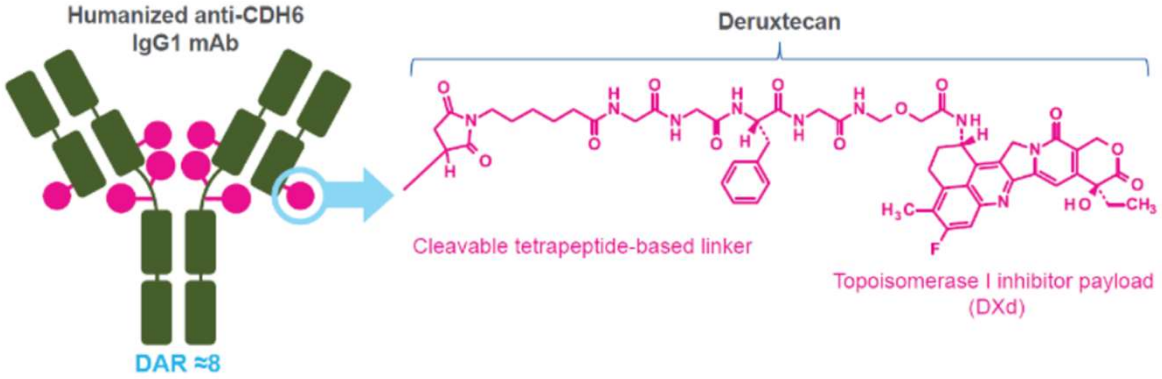
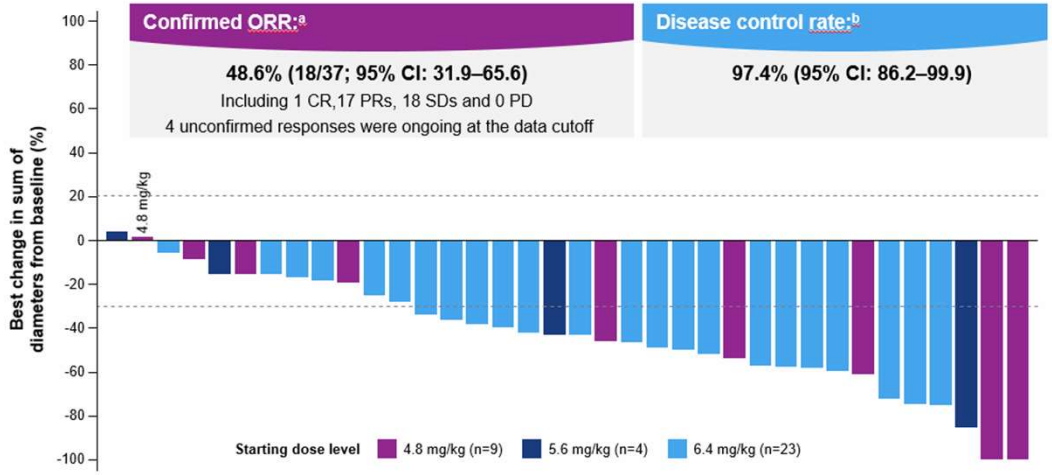
Targeting CDH6 in OC: What Do We Know So Far?

	Raludotatug deruxtecan (DS-6000)[1, 2]
Payload	Topoisomerase 1 inhibitor (DXd)
DAR	8
Linker	Cleavable tetrapeptide based linker
Trial	NCT04707248





Median DOR:[a]

11.2 months (95% CI: 3.1–NE)
Median (range) FU: 6.7 months (1.4–16.8)

Median TTR:[a]

5.7 weeks (95% CI: 5.3–11.4)

Median PFS:[b]

8.1 months (95% CI: 5.3–NE)
Median (range) FU: 4.0 months (0–25.1)

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1. Moore K, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.;
2. NCT04707248. Accessed from: https://clinicaltrials.gov/study/NCT04707248?cond=NCT04707248&rank=1.

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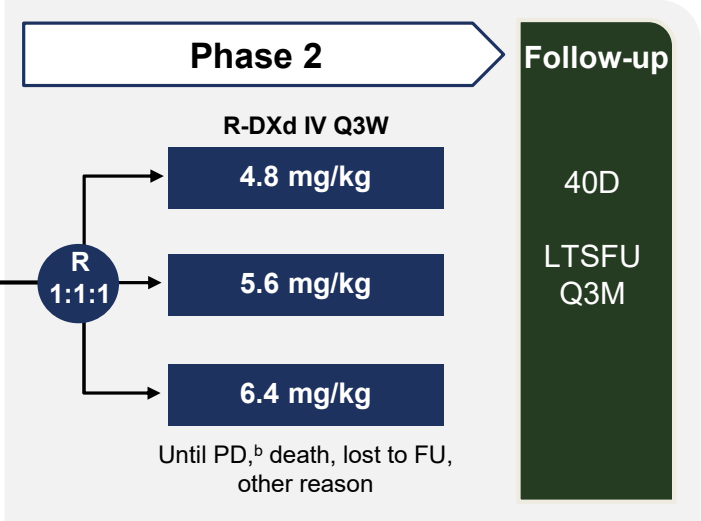
REJOICE-Ovarian01/GOG-3096: Phase 2/3 Randomized Study of R-DXd in Platinum-Resistant EOC

Key eligibility criteria:

- High-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- 1−3 prior LOT (inc. bevacizumab)
- Platinum-resistant disease
- Prior MIRV if high FRα[a]
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with linked TOPO I inhibitor
- Patients with primary platinum-refractory disease are not eligible

Stratification:

- Number of prior LOT (1 vs 2/3)
- CDH6 expression (high vs low)
- TPC (paclitaxel vs others; *Ph 3 only*)

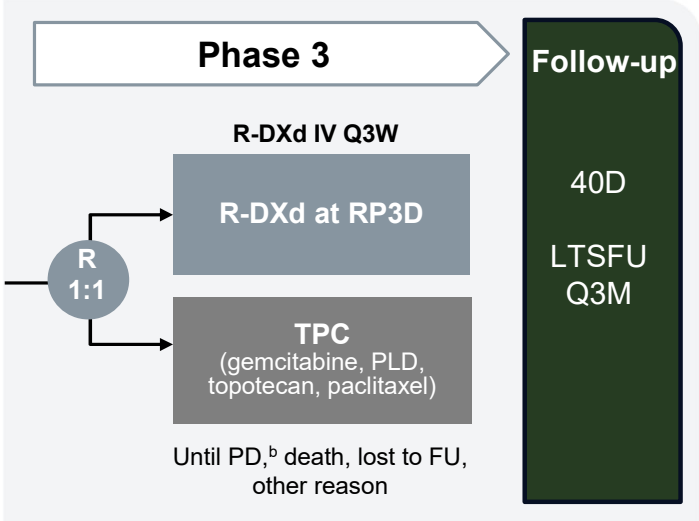


Primary endpoints:

- ORR per BICR[b]

Key secondary endpoints:

- ORR per inv[b]
- DOR



Primary endpoints:

- ORR per BICR[b]
- PFS per BICR[b]

Key secondary endpoints:

- OS
- QOL

NCT06161025

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NCT06161025. Accessed from: https://clinicaltrials.gov/study/NCT06161025?term=NCT06161025&rank=1.

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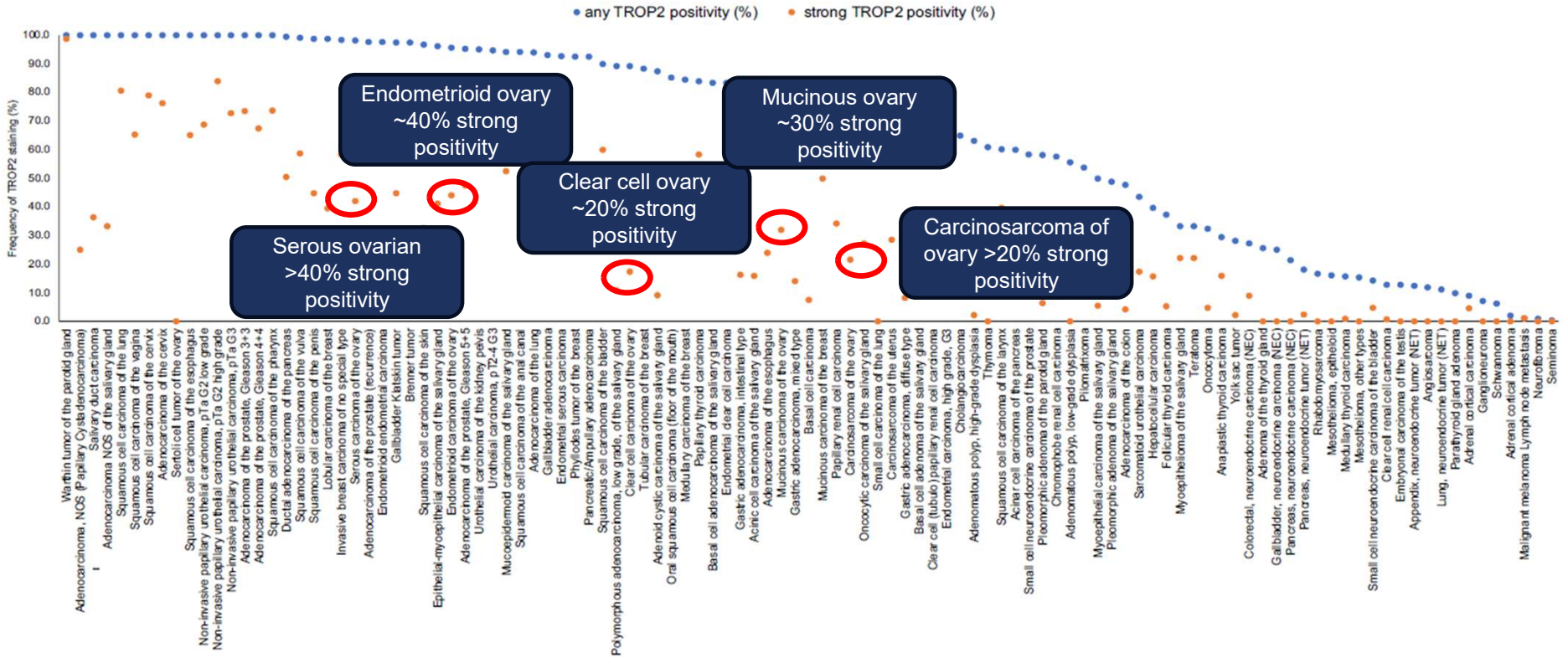
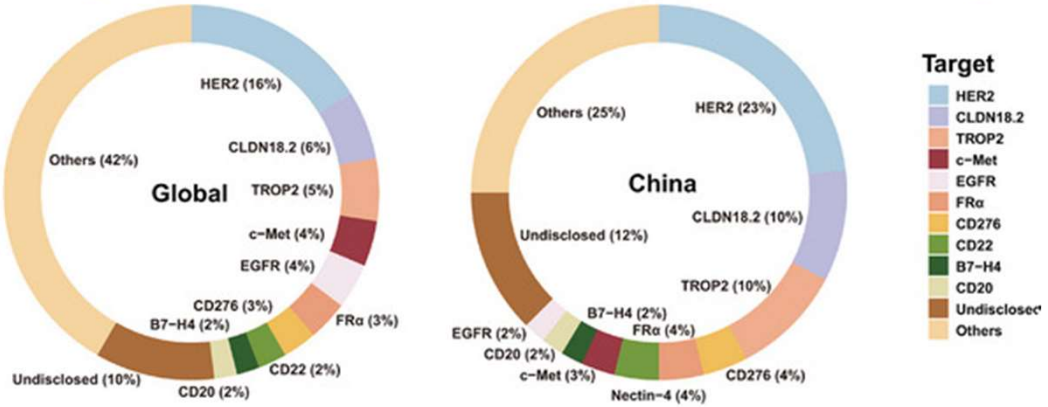
Ovarian Cancer: Is TROP2 a Relevant Target?

Ranking order of TROP2 immuno-staining in cancers. Both the frequency of positive cases (blue dots) and the frequency of strongly positive cases (orange dots) are shown.



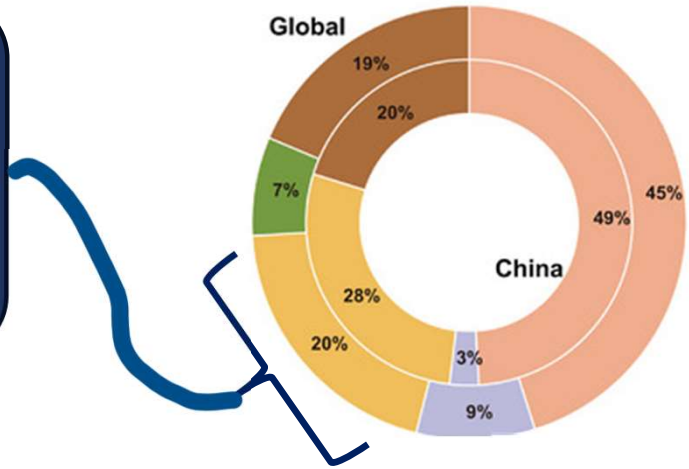
Dum D, et al. *Ann Oncol.* (2022);33(suppl_7):S27-S54. doi: 10.1016/annonc/annonc1037.

There are Almost 190 ADCs in Development Globally, Many with Targets Relevant to Gynecologic Cancers



The diversity of targets continues to increase

And while anti-tubulins still comprise the majority of ADCs, anti-camptothecins are on the rise



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Ruan DY, et al. *Cancer Commun.* 2024;44(1):3-22.

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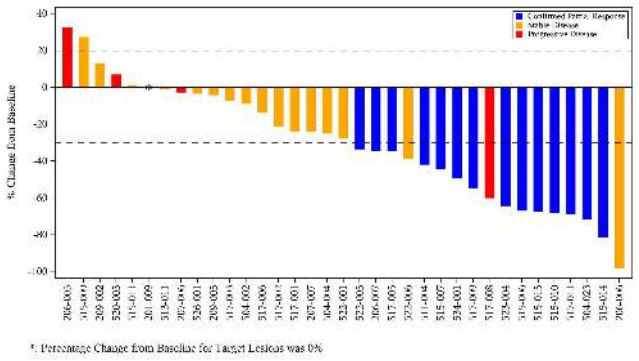
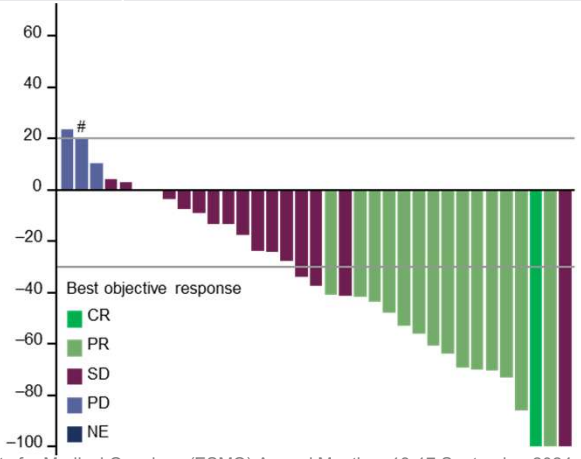
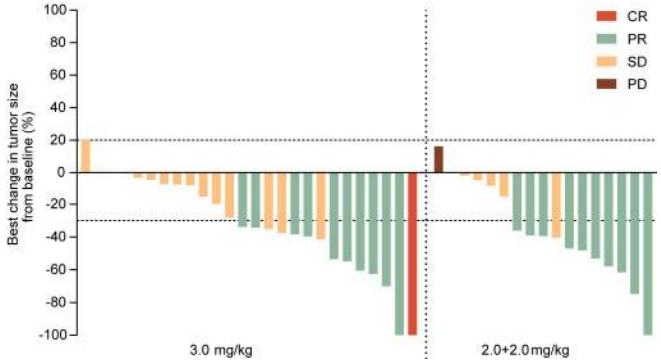
Targeting TROP2 in Ovarian Cancer

	Sacituzumab tirumotecan (MK-2870) 5mg/kg D1, D15 N=35 (PROC), **NCT06049212**	Datopotamab deruxtecan N=26 (PROC) **NCT05489211**	SHR-A1921[2] Q21 day dosing 3.0mg/kg (N=26) D1, D8 2.0mg/kg (N=20), **NCT05154604**
Payload	Belotecan derivative Topoisomerase I	Topoisomerase 1- deruxtecan	Topoisomerase 1 (proprietary SHR9265)
ORR (PROC)	37.1% (PROC)	34.6% (95% CI 17.2- 55.7)	42.3% (95% CI 23.4-63.1) 58.8% (95% CI 32.9-81.6)
DOR (PROC)	5.3 months (2.1, 24.4+)	5.6 months (2.9-NC)	9.9 months (4.5-NC) 6.3 months (3.0-NC)
mPFS	6.0 months (95% CI 3.9-7.3) (inclusive of PSOC)	5.6 months (inclusive of PSOC)	7.9 (4.2-NR) 6.9 (4.2-9.6)







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1. Wang D, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain [Abstract 715M0].; 2. Oaknin A, et al. Presented at ESMO 2024. [Abstract 714M0].; 3. He N, et al. *AACR*. 2023,April;LB030;Vol 83,Issue 8,S15.

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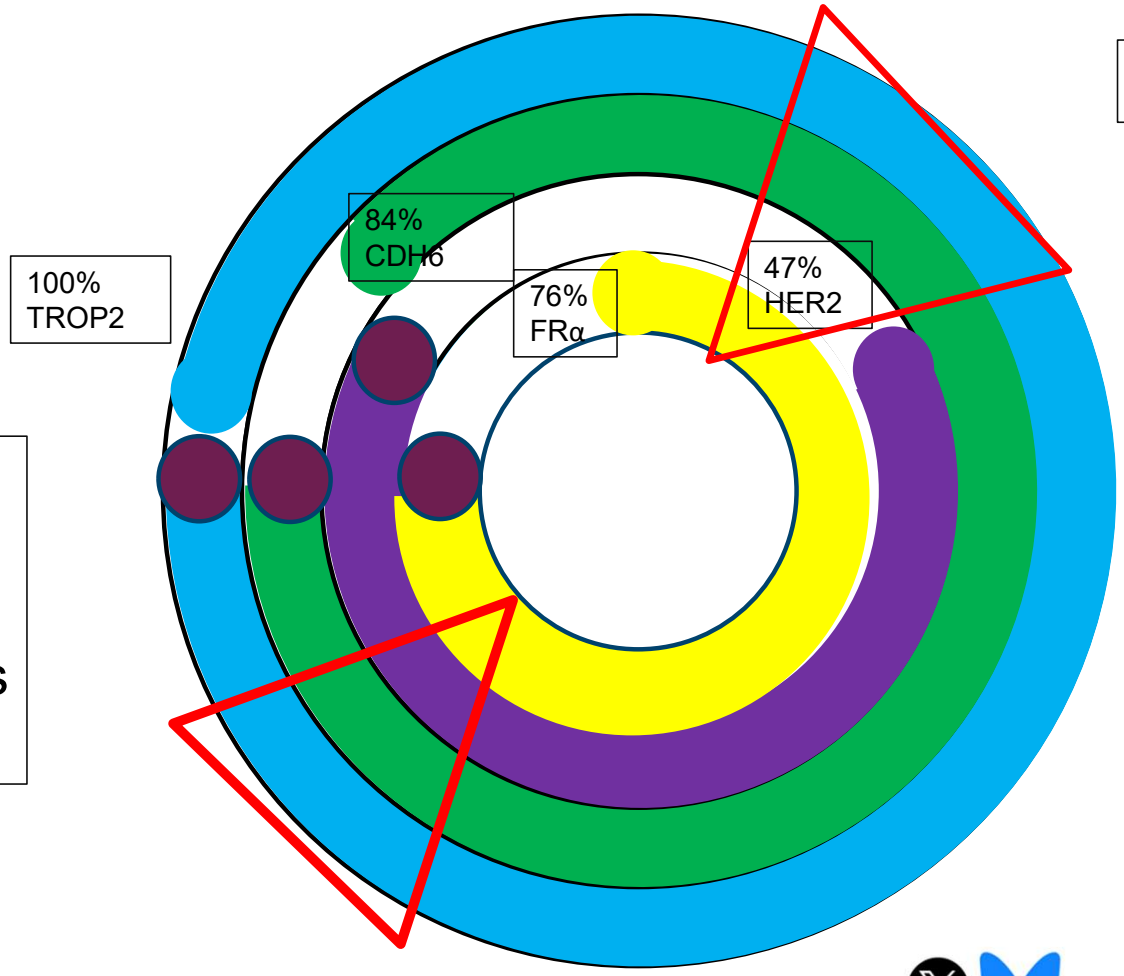
Targeting HER2, FRα, CDH6, and TROP2

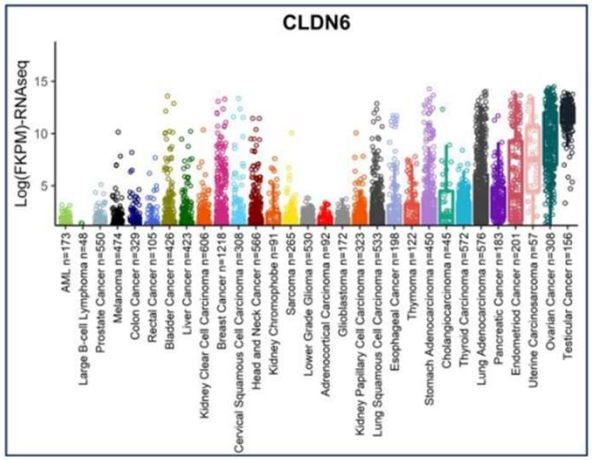


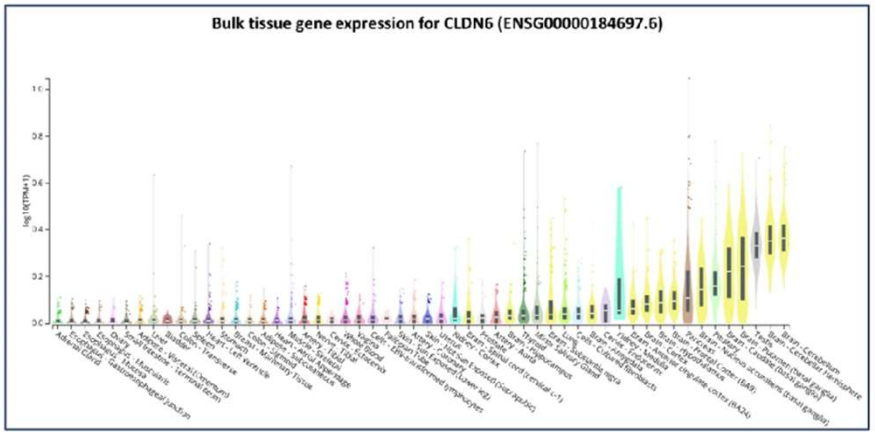
How might you select treatments for a patient whose tumor falls here?

Vs here?

Konecny G, et al. *J Clin Oncol*. 2023;41,S16,Abstract 3082.; NCT05103683 via ClinicalTrials.gov.

Targeting Claudin 6 in Ovarian Cancer: Why?



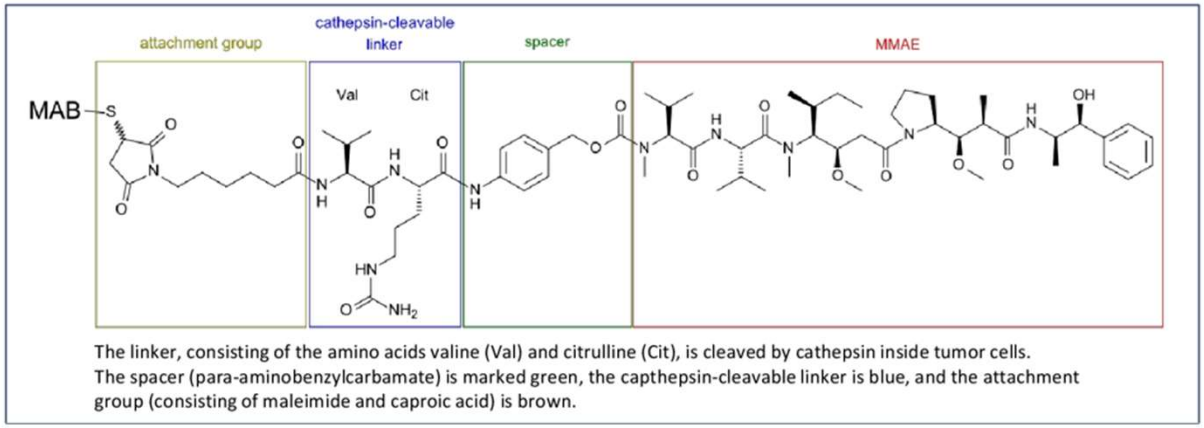


- Claudin 6 is a transmembrane protein that is important for cell to cell connectivity
- Highly overexpressed in many solid tumors – including ovary – and importantly, has little to no expression on normal tissues
- May be closest to a tumor **specific** antigen as opposed to tumor associated antigen among the solid tumor targets

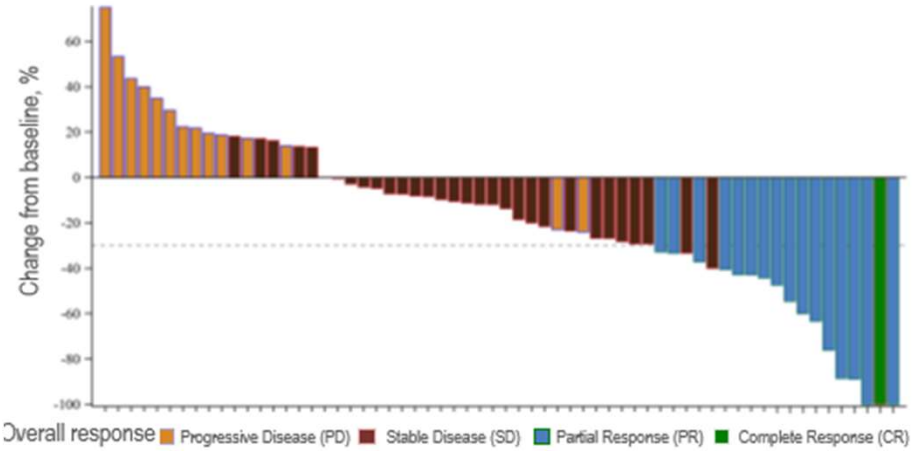
Konecny G, et al. *J Clin Oncol*. 2023;41,S16, [Abstract 3082].; NCT05103683 via ClinicalTrials.gov.

Targeting Claudin 6 in OC: What Do We Know So Far?

	TORL-1-23[1,2]
Payload	MMAE
DAR	TBD
Linker	Cathepsin hydrolysable dipeptide VC linker
Trial	NCT05103683



The linker, consisting of the amino acids valine (Val) and citrulline (Cit), is cleaved by cathepsin inside tumor cells. The spacer (para-aminobenzylcarbamate) is marked green, the capthepsin-cleavable linker is blue, and the attachment group (consisting of maleimide and caproic acid) is brown.



- 50% at 2.4 mg/kg in CLDN+
- 42% at 3.0 mg/kg in CLDN+
- 45% ≥ Grade 3 neutropenia – *now given with G-CSF…*

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Konecny G, et al. *J Clin Oncol.* 2023;41,S16,Abstract 3082.; NCT05103683 via ClinicalTrials.gov.

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Sequencing of ADCs in PROC and PSOC Must Be Considered – Even 1L – *Context is important*

Patient Demographics

Variable	Patients (n = 419)
Age (median, ±SD)	54 (± 10.54)
Initial Stage	
I	34 (8.1%)
II	21 (5.0%)
III	166 (39.6%)
IV	197 (47.0%)
Unknown	1 (0.3%)
Histology	
HGSC	332 (79.2%)
Endometrioid	12 (2.9%)
Clear cell	34 (8.1%)
Mucinous	15 (3.6%)
Others*	26 (6.2%)
BRCA status (n=191)	
HRp	54 (27.7%)
BRCAm	76 (38.7%)
BRCAwt HRD	65 (33.5%)

* Others: sarcoma, poorly differentiated carcinoma, etc

HER2 IHC and BRCA mutation/HRD status in HGSC and high-grade endometrioid carcinoma (p-value 0.005822**)

HER2	HRp	BRCAm/HRD
0/1+	55 (94.8%)	115 (79.3%)
2+/3+	3 (5.2%)	30 (20.7%)
Sum	58	145

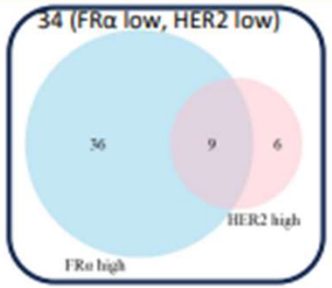
*HRp; Homologous recombination proficiency

Expression of HER2 IHC according to histology in OC (p-value 0.002794***)

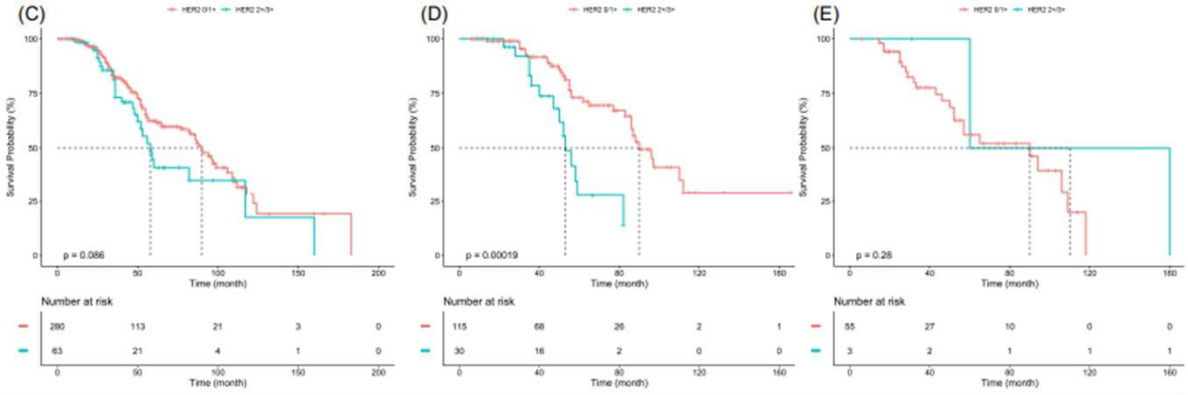
HER2	HGSC	Endometrioid	Clear cell	Mucinous	Others
0	204 (63.0%)	8 (66.7%)	12 (36.4%)	5 (33.3%)	17 (65.4%)
1+	66 (18.3%)	3 (25.0%)	7 (21.2%)	2 (13.3%)	2 (7.7%)
2+	43 (13.4%)	1 (8.3%)	11 (33.3%)	4 (26.7%)	6 (23.1%)
3+	19 (5.3%)	0 (0.0%)	4 (9.1%)	4 (26.7%)	1 (3.8%)
Total	332	12	34	15	26

- HER2 IHC and FRα expression

*FRα high: > 75%
HER2 high: 3+



Overall survival for patients with HGSC and high-grade endometrioid carcinoma: (C) all patients, (D) those with BRCAm/HRD, and (E) those with HRp.



Lee D, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

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ADCS for Platinum Sensitive Disease: It's time to Optimize Regimens in OC in a Post PARPi World

	Sacituzumab tirumotecan 5mg/kg D1, D15 N=5 (PSOC)	Datopotamab deruxtecan N=9 (PSOC)	Mirvetuximab soravtansine N=79
Payload	Belotecan derivative Topoisomerase I	Topoisomerase 1- deruxtecan	DM4
DAR	7.4	4	4
Linker	Sulfonyl pyrimidine CL2A-carbonate linker	Cleavable tetrapeptide based linker	Cleavable linker
Trial	NCT06049212	NCT05489211	NCT05041257
ORR	60% (PSOC N=5)	66.7% (PSOC N=9)	51.9% (95%CI 40.4-63.3)
DOR	ND	ND	8.25 (95% CI 5.55-10.78)
mPFS	ND	ND	6.93 (95% CI 5.85-9.59)

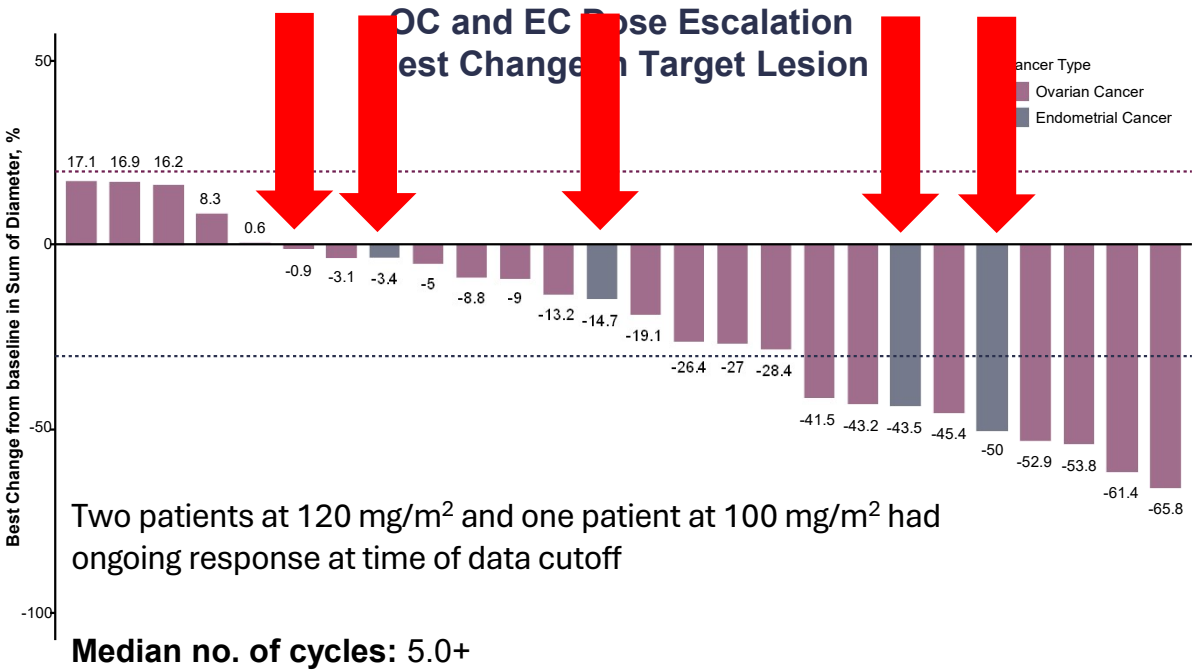
EC: Similar Targets, but Molecular Context is Even More Important

Target	Name	Payload	Payload	DAR	Linker	Development stage
HER2	Trastuzumab deruxtecan	Topo1i	deruxtecan	8	Cleavable	Phase II – FDA acc appr
	DB-1303 (BNT323)	Topo1i	P1003	8	Cleavable	Phase I/IIA – FDA BTD
	Trastuzumab duocarmazine	DNA alkylating	duocarmazine	2.8	Cleavable	Phase II
	Disitamab vedotin (RC48)	Anti-microtubule	MMAE	4	Cleavable	Phase II
FRα	Mirvetuximab soravtansine	Anti-microtubule	DM4	3.5	Cleavable	Phase II
	Luveltamab tazevibulin (STRO-002)	Anti-microtubule	SC209	4	Cleavable	Phase I/IIA
	Rinatabart sesutecan (Rina-S, PRO1184)	Topo1i	exatecan	8	Cleavable	Phase I/II
	IMGN151	Anti-microtubule	DM21	3.5	Cleavable	Phase I
TROP2	Sacituzumab govitecan (IMMU-132)	Topo1i	SN38	7.6	Cleavable	Phase II
	Sacituzumab tirumotecan (MK-2870)	Topo1i	tirumotecan	7.4	Cleavable	Phase III
	Datopotamab deruxtecan (DS-1062)	Topo1i	deruxtecan	4	Cleavable	Phase II
	LCB84	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
B7-H4	SGN-B7H4V	Anti-microtubule	MMAE	4	Cleavable	Phase I
	HS-20089	Topo1i	undisclosed	6	Cleavable	Phase II
	XMT-1660	Anti-microtubule	MMAF	6	Cleavable	Phase I
	AZD8205	Topo1i	AZ14170133	8	Cleavable	Phase I/IIA
B7-H3	Ifinatamab veruxtecan (DS-7300a)	Topo1i	deruxtecan	4	Cleavable	Phase I
TF	Tisotumab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase II
	XB002	Anti-microtubule	MMAE	3.3	Cleavable	Phase I
AXL	Enapotamab vedotin	Anti-microtubule	MMAE	4	Cleavable	Phase I/II
Claudin6	TORL-1–23	Anti-microtubule	MMAE	?	Cleavable	Phase I

Rinatabart Sesutecan Antitumor Activity | OC, EC – Dose Escalation

Rina-S showed encouraging antitumor activity in heavily pretreated patients with OC and EC

Part A: OC and EC Dose Escalation	
Rina-S (100 mg/m² and 120 mg/m²) n = 26[a]	
Confirmed ORR,[b] % (95% CI)	30.8 (14.3-51.8)
Best overall response,[b] n (%)	
PR	8 (30.8)
SD	15 (57.7)
PD	3 (11.5)
DCR, % (95% CI)	88.5 (69.8-97.6)
Median DOR, weeks (95% CI)	35.3 (20.14-NE)



Two patients at 120 mg/m² and one patient at 100 mg/m² had ongoing response at time of data cutoff

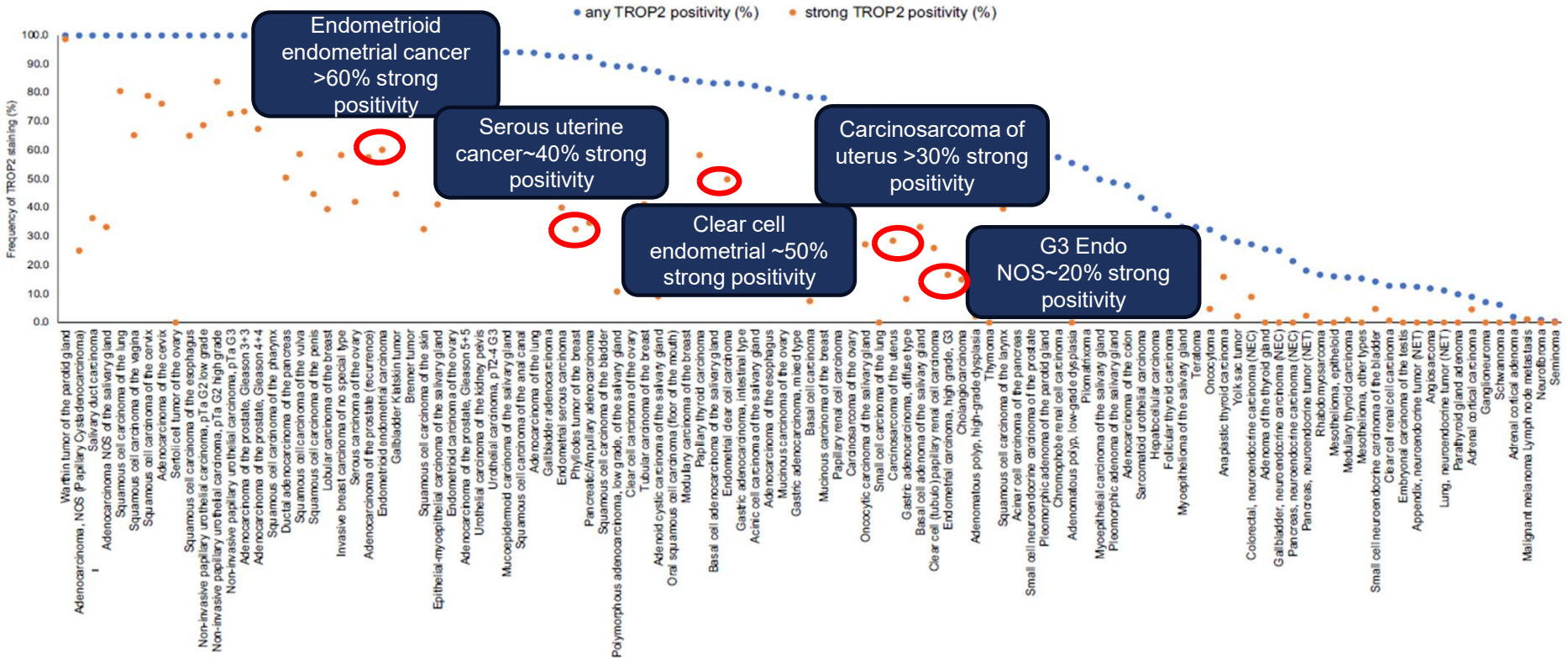
Median no. of cycles: 5.0+

[a]Response-evaluable population. The response evaluable population set includes all treated patients who had a baseline and at least 1 evaluable postbaseline tumor assessment, or who had documented progression of disease at any time after the first dose of Rina-S. Response assessment per RECIST v1.1. [b]Based on investigator assessment. [c]For all patients who received Rina-S 100 mg/m² or 120 mg/m². [d]For patients with OC and EC who received Rina-S 100 mg/m² or 120 mg/m².
CI confidence interval; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Rina-S, rinatabart sesutecan; SD, stable disease.

Lee EK, et al. Presented at: Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.

TROP2 ADCS in EC: Is this a valid target and where does it fit?

Ranking order of TROP2 immuno-staining in cancers. Both the frequency of positive cases (blue dots) and the frequency of strongly positive cases (orange dots) are shown.



Dum D, et al. *Ann Oncol.* 2022;33(S7):S27-S54. doi: 10.1016/annonc/annonc1037

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Targeting TROP2 in Endometrial Cancer

	Sacituzumab govitecan 10mg/kg Day 1, 8 N=41	Sacituzumab tirumotecan 5mg/kg D 1, 15 N=44	Datopotamab deruxtecan 6mg/kg q 21 days N=40
Payload	SN3 – Topoisomerase 1	Belotecan derivative Topoisomerase I	Topoisomerase 1- deruxtecan
DAR	7.6	7.4	4
Linker	pH sensitive hydrolysable linker	Sulfonyl pyrimidine CL2A-carbonate linker	Cleavable tetrapeptide based linker
Trial	NCT03964727 (TROPICS 03)	NCT06049212	NCT05489211 (TROPION-PanTumor03)
Prior CPI/mLOT	85.4%/3 (1-6)	36.4%/ 53% ≥ 2 LOT	22.5%/ 47.5% ≥ 2 LOT
ORR (PROC)	22% (95% CI 11-38)	27.3%	27.5% (95% CI 14.6-43.9)
DOR (PROC)	8.8 mo (95% CI 2.8- NE)	5.7 (3.8, 7.4+) range	16.4 months (7.1 – NC)
mPFS	4.8 mo (95% CI 2.8- 9.8)	5.7 months (95% CI 3.7-9.4)	6.3 months (2.8 – NC)

The ORR and mPFS across studies look very similar: How do we distinguish between these agents and should we be using biomarker selection?

Santin A, et al. *J Clin Oncol.* 2024.; Wang D, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain.; Oaknin A, et al. Presented at ESMO 2024.; He N, et al. *AACR.* 2023,April;LB030;Vol 83,Issue 8,S15.

In the two activated RP3 studies – the comparator is ineffective, standard of care, monotherapy chemo. With an expected ORR of 15% and median PFS of < 4 months – maybe a biomarker isn't necessary?

Phase 3 ENGOT-en23/GOG-3095/MK-2870-005[1]
N=710

Key Eligibility Criteria

- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- Has not received >3 prior lines of therapy

R

MK-2870 4 mg/kg IV on day 1 of each 14-day cycle

Doxorubicin 60 mg/m² IV on day 1 of each 21-day cycle
or
Paclitaxel 80 mg/m² IV on days 1, 8, and 15 of each 28-day cycle

NCT06132958

- **Primary endpoints**: PFS, OS
- **Secondary endpoints**: ORR, DOR, safety, HRQOL

Phase 3 GOG-3104/ENGOT-en26
N=520

Key Eligibility Criteria

- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- Has not received >3 prior lines of therapy

R

Sacituzumab govitecan 10mg/kg D1, D8

Doxorubicin 60 mg/m² IV on day 1 of each 21-day cycle
or
Paclitaxel 80 mg/m² IV on days 1, 8, and 15 of each 28-day cycle

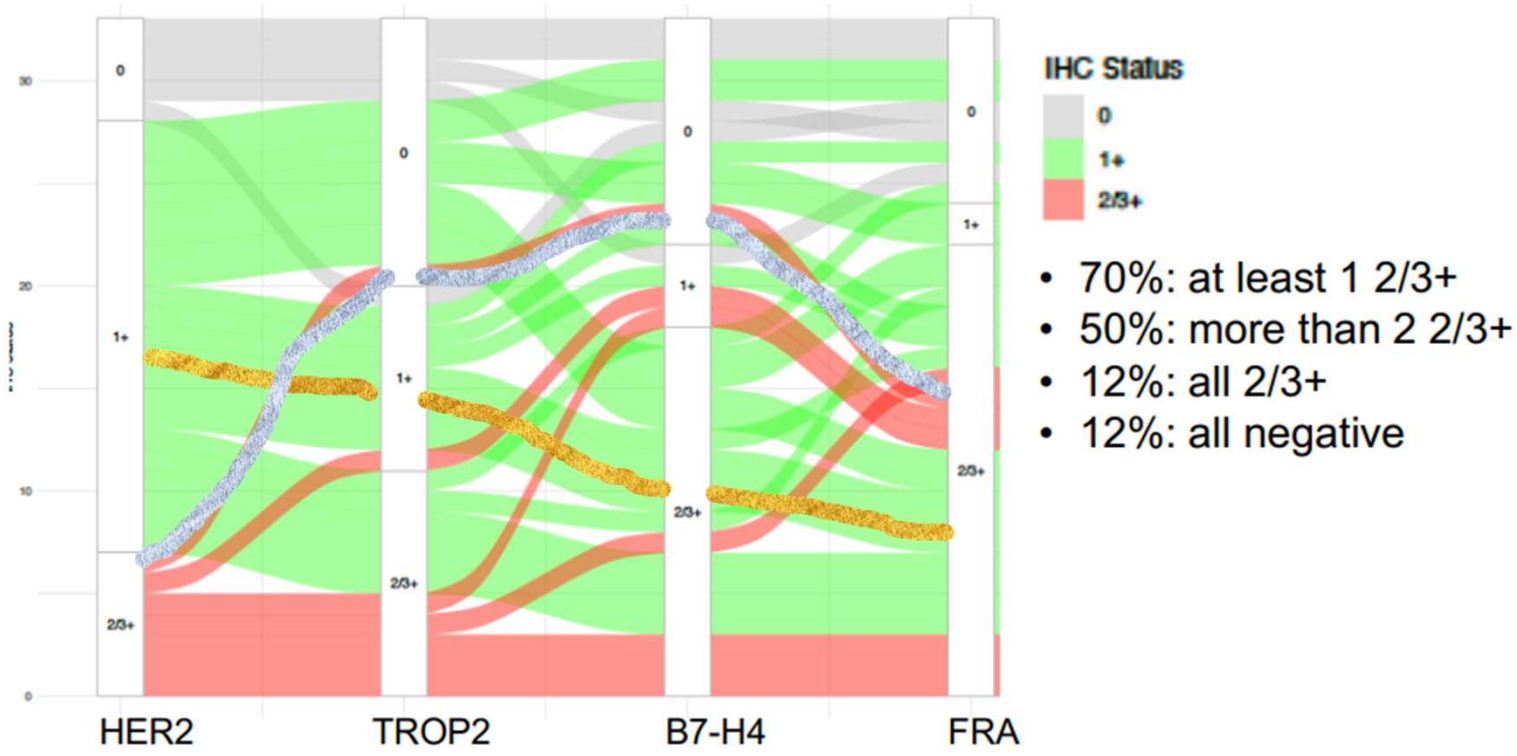
NCT06486441

- **Primary endpoints**: PFS, OS
- **Secondary endpoints**: ORR, DOR, safety, HRQOL

1. NCT06132958 via ClinicalTrials.gov. Accessed April 29, 2024.; 2. NCT05382268 via ClinicalTrials.gov. Accessed Sept 1, 2024 .

However – if a patient has several ADC options in this space – biomarkers become more relevant for optimal selection of the right medicine and the right time

Overlap of each target expression in high-grade EC

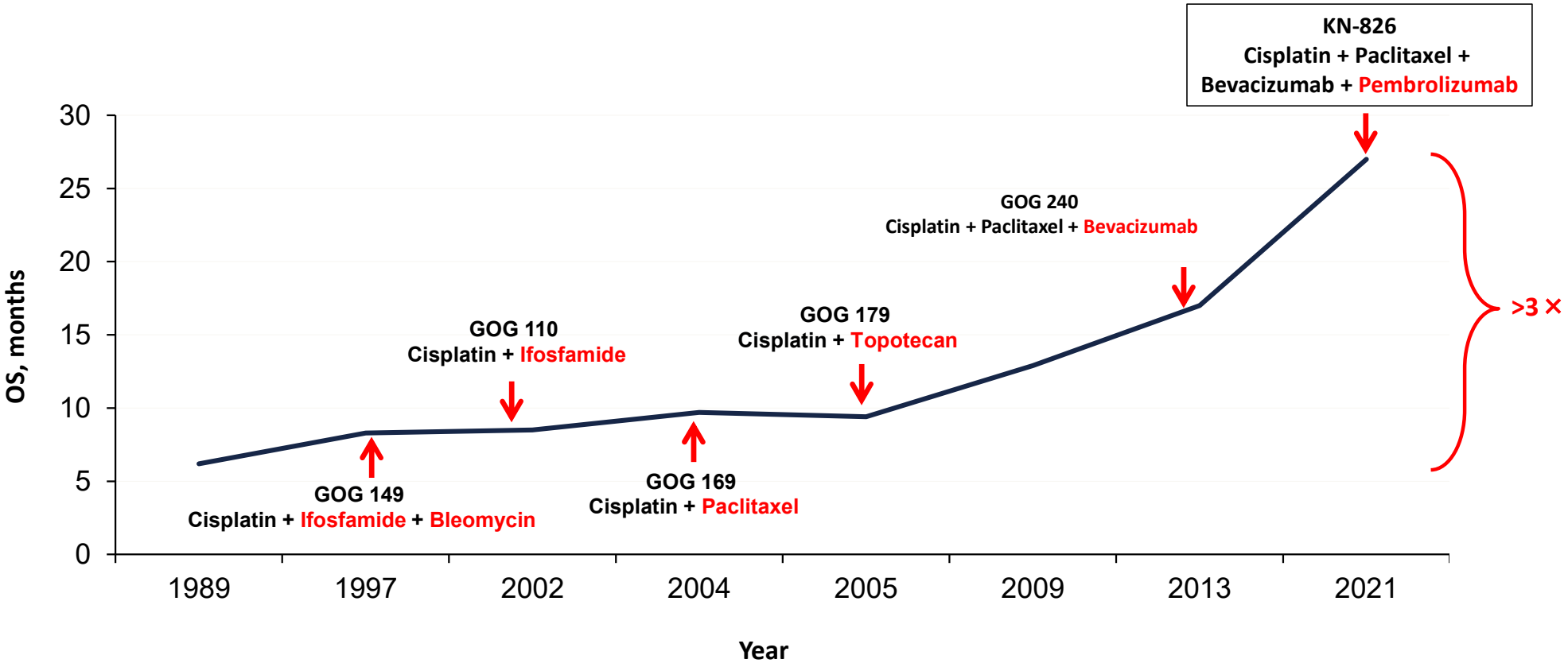


- 70%: at least 1 2/3+
- 50%: more than 2 2/3+
- 12%: all 2/3+
- 12%: all negative

Hasegawa, Yoshida, Yagishita unpublished data

Hasegawa, Yoshida, Yagisita unpublished data, *Shared with permission.*

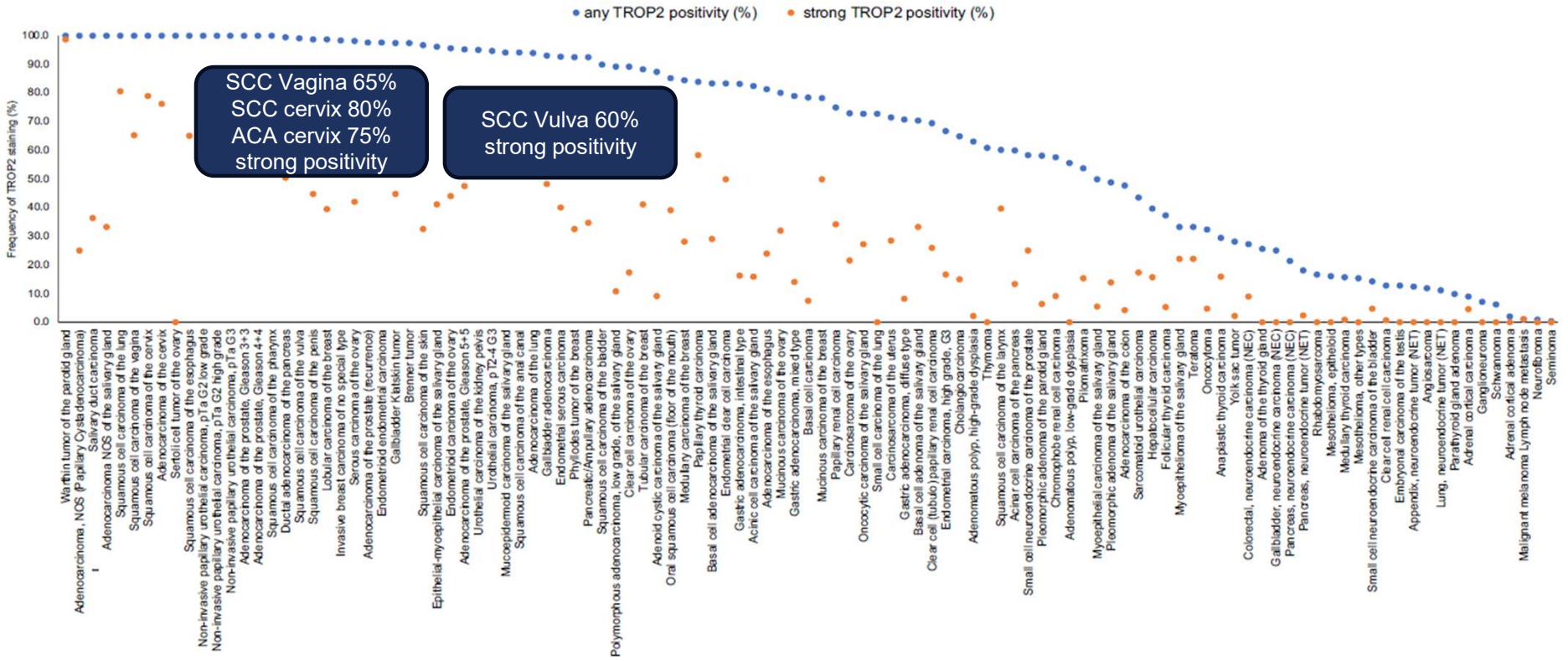
Improving OS in Recurrent or Metastatic Cervical Cancer: Where Do ADCs Fit in the Context of CC?



Leath CA, et al. *Gynecol Oncol*. 2018;150:391-397; Colombo N, et al. *N Engl J Med*. 2021;385:1856-1867.

Cervical Cancer: Is TROP2 a Relevant Target?

Ranking order of TROP2 immuno-staining in cancers. Both the frequency of positive cases (blue dots) and the frequency of strongly positive cases (orange dots) are shown.



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Dum D, et al. *Ann Oncol*. 2022;33(S7):S578. doi: 10.1016/j.annonc.2022.07.115.

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What is the Efficacy of Targeting TROP2?

	Sacituzumab govitecan (N=18)	Sacituzumab tirumotecan (MK-2870) plus pembrolizumab N=40
Payload	SN3 – Topoisomerase 1	Belotecan derivative Topoisomerase I
DAR	7.6	7.4
Linker	pH sensitive hydrolysable linker	Sulfonyl pyrimidine CL2A-carbonate linker
Trial	NCT05838521	NCT05642780
Prior Bev	61%	52.6%
Prior CPI	78%	42.1%
ORR	50%	57.9% (95% CI 33.4-66.6)
DOR	9.2 months	NR (NE, NE)
mPFS	8.1 months	NR (95% CI 5.6 – NE)

My comments:

1. **WOW!!!!**
2. Do we need pembrolizumab here? Is this more than just independent drug action?

Independent Drug Action Model

$P_{AB}(t) = P_A(t) + P_B(t) \times (1-P_A(t))$

$P_{AB}(t) = .50 + .164 \times (1-.50) = .582$ or **58.2%**

ORR: Saci tirum + Pembro: 57.9% (95% CI 33.4-66.6)

This estimates that this is just independent drug effect and not additivity or synergy

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An J, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, CA USA., Wu et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain., Plana D, et al. *Cancer Discov*. 2022.

What is the Efficacy of Targeting TROP2? *In Context With Other ADCs*

	Sacituzumab govitecan (N=18)	Sacituzumab tirumotecan (MK-2870) + Pembro N=40	Tisotumab vedotin N=253	9MW2821 (Nectin 4) N=45	Trastuzumab deruxtecan (N=40)
Payload	SN3 – Topoisomerase 1	Belotecan derivative Topoisomerase I	MMAE	MMAE	DXd
DAR	7.6	7.4	4	4	8
Linker	pH sensitive hydrolysable linker	Sulfonyl pyrimidine CL2A-carbonate linker	protease-cleavable valine-citrulline (vc) linker	valine–citrulline (VC) dipeptide linker called IDconnect™	cleavable tetrapeptide-based linker
Trial	NCT05838521	NCT05642780	NCT04697628	NCT05216965	NCT04482309
Prior Bev	61%	52.6%	64.8%	51%	NR
Prior CPI	78%	42.1%	28.1%	58%	NR
ORR	50%	57.9% (95% CI 33.4-66.6)	17.8%	37.8 (95% CI 24-54)	75% HER2 3+ 40% HER2 2+
DOR	9.2 months	NR (NE, NE)	5.3 months	NR	
mPFS	8.1 months	NR (95% CI 5.6 – NE)	4.2 months	4.0 (95% CI 3.75-5.68)	NR (95% CI 3.9 – NR) 4.8 (95% CI 2.7-5.7)

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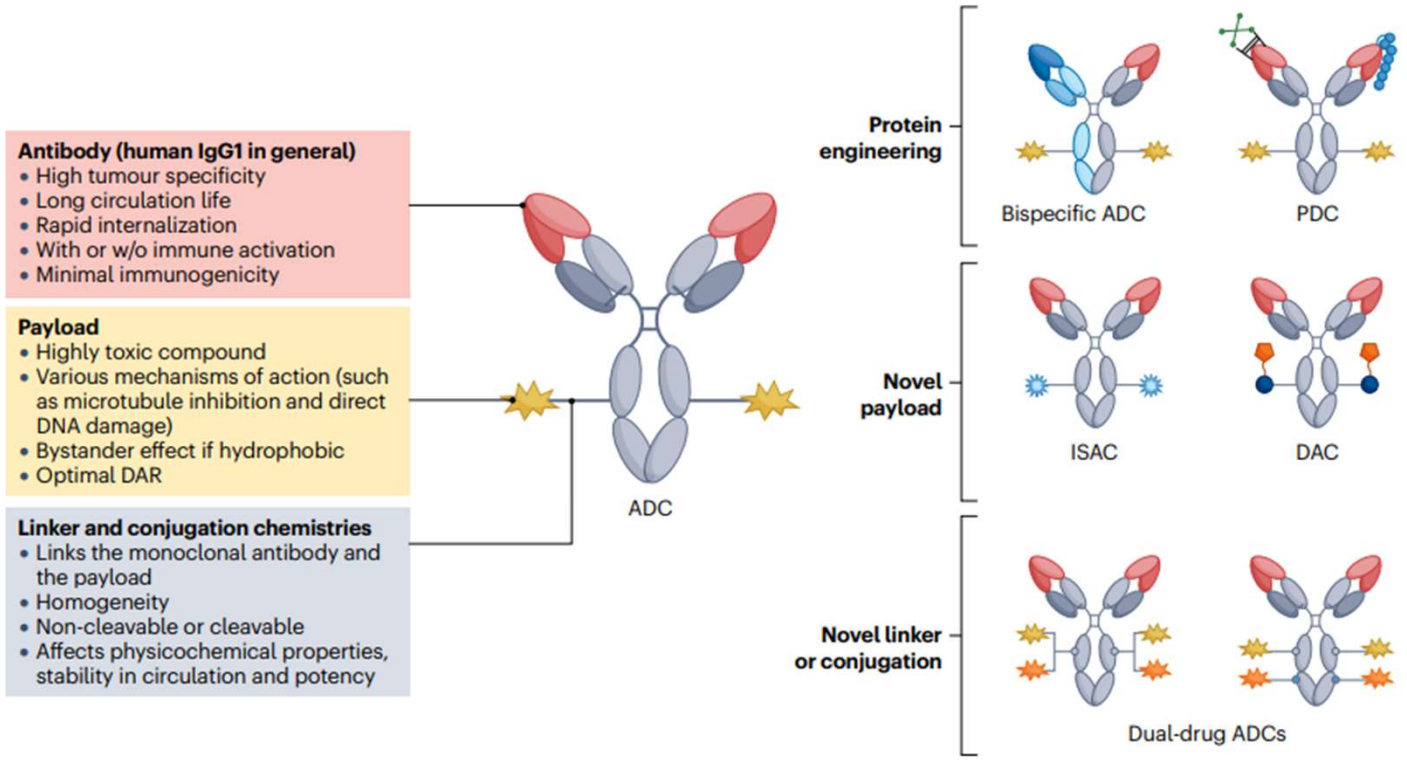
An J, et al. Presented at: Society of Gynecologic Oncology's (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, CA USA., Wu et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 13-17 September 2024; Barcelona, Spain., Vergote I, et al. *NEJM*. 2024.; Zhang et al. J Clin Oncol Vol 42, No 16 suppl 2024; Makker V, et al. SGO 2024, Meric-Bernstam F, et al. ESMO 2023.

What is Next?

Further tumor specificity may be possible through targeting true tumor specific antigens- recognized via structural variations such as truncation or nicking.
Nicked TROP2 is one example under study



Tsuchikama K, et al. *Nat Rev Clin Oncol.* 2024;21:203–223. doi: 10.1038/s41571-023-00850-2

Conclusions:

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Transforming the standard of care

In the past 1-2 years we have seen a panoply of new ADCs – many with very promising efficacy signals in patients with limited options. Now the hard work begins.

- Several studies were performed mainly or entirely in China so will be important to **expand enrollment globally** and **re-evaluate efficacy**
- **Dose Optimization** will be **key** for each disease type and agent - how much and how often to maximize benefit and minimize toxicity
- **Regimen Optimization** is upon us – where do we use these assets? All in R/M? Or moving up to PSOC? Maintenance – what data do we need to get the timing right?
- **Sequencing is a huge opportunity** for our patients. Biomarkers have to be evaluated, validated, and built into trials
- **New constructs will have to be evaluated carefully** – all comer studies may not give us the information we need to really craft scientifically based directions for drug development with these exciting agents

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